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Modern Cancer Research

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APPROACHES to the cancer problem, as it is now visualized, are indeed diverse. The aid of all the sciences is being freely called upon by the medical profession which, realizing that this is "the age of cancer progress," is resolved to "maintain at the highest level the momentum now gained in this field." The ramifications of the interest in cancer reach into many branches of human knowledge and form a broad basis which assures sound progress, providing the resources be not dissipated over so wide a territory as to lose practical value. Experimental investigation requires the labours of chemists, physicists, biologists, eugenists, physiologists and pathologists for, to make progress in this complex subject, specialization is imperative.

A vast body of knowledge, accumulated from investigations into the fundamental problems of cancer in the past 40 years, has cleared away much of the mystery associated with the disease. In the first scientific report of the Imperial Cancer Research Fund in 1904 was the statement that ". . . fundamental common attributes relate the malignant new growths to one another in a natural group. The explanation of these common fundamental characters is bound up with the mode of origin of malignant new growths and is the problem awaiting solution, to be followed by the specific explanation of the individual variations, as its natural corollary." Although, in its broader aspects, the same problem still confronts us, it has been more accurately defined and brought to a practical stage by experimental pathology. The mode of origin of malignant new growths, if it be a single factor, has not yet been discovered but numerous modes of production of malignancy *in vivo* and *in vitro* are now available. A study of the relationship of these various ways of producing cancer is one of the most urgent needs at present.

THE VIRUS HYPOTHESIS

The results of certain bacteriological investigations tend to support a virus hypothesis of the origin of cancer. Recently, interest in the virus origin has been greatly revived and valuable possibilities have been disclosed.

Following the discovery by Rous, in 1910, that a sarcoma occurring

spontaneously in a domestic fowl was transmissible to other fowls of the same species by a cell-free filtrate, numerous investigators sought to attribute similar properties to mammalian tumors. With the exception of a lymphosarcoma of dogs and a papillocarcinoma of rabbits, it has not been possible to inoculate mammalian tumors by any other method than cell transfer.

A long series of experiments, performed in England and America, designed to determine the nature of the agents in the Rous and allied tumors, have disclosed some interesting features. Incredibly small amounts of the filtrates were found to be capable of stimulating normal cells to assume malignant changes and to form tumors. In behaviour and in appearance under the ultra-violet ultra-microscope, marked similarity to known viruses was pointed out by Gye and later workers. Both the Rous and Shope papilloma agents have been demonstrated as particulate in nature and approaching the dimensions of 90 uu. in diameter.

More recently, the known viruses have been subjected to closer scrutiny and the crystalline nature of some of them revealed. Coincident work on the Rous agent has also disclosed its chemical nature. However, in the light of modern conceptions the chemical, non-living, protein molecules grade imperceptibly into the living viruses which are of quite comparable molecular complexity, so that it is impossible to say, as yet, in what sphere the Rous agent belongs.

The various "agents" stimulate the production of specific agglutinins in tumor-bearing animals, indicating that they are, in whole or in part, extrinsic to the animal. Certain instances of tumor agent-neutralizing antibodies in normal fowls have been recorded, a phenomenon which is analogous to the occasional spontaneous regressions of mammalian tumors.

One view of the virus hypothesis is that this extrinsic, antibody-producing agent requires the presence of a second specific factor in order to initiate tumor growth. In support of this proposal is the fact that the intravenous injection of the virus fails to produce growths, although it can be readily isolated from all the tissues of the body. If, however, a muscle or other tissue be traumatized after injection of the virus then a tumor develops at the site of the injury.

This peculiar property bears an interesting relationship to the chemicals which induce cancer. The Shope virus produces active proliferation of warts in wild rabbits. In domestic rabbits these warts often become fissured, ulcerate and develop a low-grade carcinoma. If benzpyrene, a chemical carcinogen, be rubbed on the skin of rabbits into which the virus has been injected intravenously the resulting warts are more numerous, grow more actively, and a much greater percentage become malignant.

These findings suggest the possibility of multiple factors, one of

which may be a virus, being concerned in the origin of some cancers. Viruses may come to be considered as a partial factor in the etiology of certain epithelial tumors of man for the infectious behaviour of some papillary mucous membrane tumors has long been recognized clinically.

CHEMICAL CARCINOGENESIS

One of the great landmarks in cancer research was the production of papillomata in rabbits by prolonged tar applications. Since the epochal report of Yamigawa and Ichikawa, in 1918, tumors have been experimentally induced by a great variety of agents. Highly potent carcinogenic chemicals have been isolated and still others have been synthesized. Leaders in the chemistry of cancer production have been Kennaway, Cook and their associates in England; Fieser, Shear and co-workers in America; and Wieland in Germany.

The active carcinogenic agent in tar was isolated in 1933 by Cook, Hewett and Hieger. It proved to be 3:4-benzpyrene. In the course of the next few years the English school synthesized a large number of related aromatic hydrocarbons for a systematic study of the relation between chemical structure and carcinogenic properties. Many of these are derivatives of 1:2-benzanthracene. All the theoretically possible derivatives have been synthesized. A new member, 9:10-dimethyl-1:2-benzanthracene, is the most active carcinogen known, producing tumors in mice within 50 days.

Substitution of simple (methyl) groups in the 10-position of the 1:2-benzanthracene system increases the carcinogenic potency while the presence of elaborate (isopropyl) groups in this position practically destroys it. Methyl cholanthrene is one of the most significant substances discovered in the course of studying cancer-producing activity. It is a derivative of 1:2-benzanthracene with substituents at positions 5 and 10 and produces cancer in mice in 2.5 months. Originally it was prepared from desoxycholic acid, a bile acid, by a four-step reaction. This fact suggested the possibility of a pathological deviation in bile or cholesterol metabolism leading to the production of a carcinogenic chemical but the presence of methyl cholanthrene has never been demonstrated in the animal body. Fieser and his collaborators have shown, however, that the 5-carbon ring characteristic of the bile acids is not essential for carcinogenicity. He has also postulated that even if methyl cholanthrene is formed in the degradation of bile acids it may be further acted upon to form an innocuous hydrocarbon. Such a conversion has not yet been accomplished in the laboratory but even modern chemistry fails to perform many chemical transformations which the tissues accomplish with ease.

Recent work has shown that carcinogenic chemicals inhibit the breakdown of cholesterol esters and possibly cause esterification of cholesterol in animals. It has been suggested that the sterols, bile acids and sex hormones, all structurally related by the five-membered ring to

methyl cholanthrene, may be involved in the incidence of some forms of spontaneous cancer but at present there is no good reason for presuming the presence of active carcinogens in the body. While most of the active substances so far examined are benzanthracene derivatives, compounds of widely different structure are also carcinogenic. Carcinogenic power, though not dependent on a specific chemical structure, may be determined by a particular kind of reactivity shared by compounds of dissimilar structure. Fieser's recent work demonstrates that all the active compounds undergo rapid change in the body and are exhausted long before tumors begin to appear, but they may initiate a complicated chain of events leading ultimately to malignant growth. He has found that "the most potent carcinogens have unique chemical properties, surpassing all other known aromatic hydrocarbons in chemical reactivity of a special kind, notably a high degree of susceptibility to substitutions of a special type and to oxidation with lead tetra-acetate." The suggestion is made that these highly active chemicals conjugate with substances present in the organism, by hydroxylation or substitution, thereby forming a basis for later cancer production in the animal body.

While the carcinogenic potency of certain substances is established, the same chemical does not uniformly produce cancer in all types of animals, nor even in all strains of a susceptible species. Some strains of mice are highly susceptible to skin cancer, chemically induced, while others, with a high incidence of spontaneous lung tumors, respond to carcinogens on the skin by developing lung tumors in greater numbers and at earlier than normal age periods. Old rabbits are liable to uterine cancer and it has been found that in many of these to which carcinogens were administered by various routes, no tumors arose at the site of application but the percentage of uterine tumors rose abruptly. Conversely, in studying a fluorescent carcinogen, Chalmers and Peacock (1938) have reported that it is excreted in the bile, urine and skin fat but produces tumors only at the site of application and never along the routes of excretion. These observations point to an inheritance factor, either chromosomal or extra-chromosomal, but certainly with a localization of malignancy. They corroborate the theory of localization characters in spontaneous tumors of all animal types and again suggest the operation of two factors, an intrinsic hereditary susceptibility and an extrinsic chemical agent.

Some chemicals entirely foreign to the animal body can also induce malignant tumors. A variety of these have been reported but in numerous cases repetition failed to substantiate early claims. Attempts to induce bladder tumor growth in animals by administering aniline dyes have finally been rewarded after many years of experiment. Increasing doses of aniline, benzidine and betanaphtylamine were given to dogs both by mouth and subcutaneously for 1½ to 2 years. Periodic cystoscopic examinations and biopsies followed the histopathological process leading to the formation of benign papillomata and finally to true

carcinoma. The time to induce these tumors is significantly long and is consistent with the observation that dye workers have been exposed for many years before developing bladder symptoms.

Another dye, amino azotoluene, produces liver tumors in rats either when administered in the diet for 10 months or when subcutaneously implanted in solid form. The high solubility of the dye in fats and lipoids may be a factor in its selective action on the liver. A recent paper reported that "butter yellow," an azo dye closely related to amino azotoluene, also induces liver tumors in rats. If this be confirmed, the discontinuance of the use of this dye would be justified.

Excessive exposure to X-rays and radium has long been known to give rise to cancerous changes in the body. The use of radioactive substances in medicine has consequently been frowned upon but no evidence of their carcinogenic action was brought forth. Now, however, there is proof that "Thorotrast" (colloidal thorium hydroxide), a radio-opaque substance injected into the brain and venous system for diagnostic purposes, is definitely carcinogenic. In the rats, mice and guinea pigs tested there was a long delay before malignant change occurred, but it finally did appear in two and one-half to three years. Since thorotrast has not been long in use it is premature to conclude that it is harmless to man as 10 to 15 years would be required before cancerous change could be expected.

Lacassagne (1932) reported the first instance of the production of malignant tumors by a naturally occurring chemical of known structure. Mammary cancer normally occurs only in female mice but Lacassagne succeeded in inducing the development of mammary cancer in male mice by long-continued treatment with large doses of oestrin. Subsequent research has shown that the carcinogenic action of the oestrogens is proportional to the dosage and that they produce cancer in other sites, namely, the cervix uteri and subcutaneous tissue.

Cramer and Horning (1938) have reported the effects of prolonged oestrone administration on mice and rats. The anterior pituitary gland enlarged with almost complete disappearance of the granular acidophil cells, the adrenals degenerated and the mammary glands progressed to malignancy. When thyrotropic hormone was given simultaneously with oestrone these changes did not occur. This result led to a test of the effect of thyrotropic hormone on spontaneous mammary cancer in mice. Female mice of a highly susceptible strain were treated with thyrotropic hormone from an early age and none of them developed tumors although they all lived well into the cancer age period. The possibility of specific prophylaxis is enticing but it must not be overestimated while so much remains to be known about the pituitary gland.

An interesting observation was made by Cook in 1933 when several synthetic carcinogens were discovered to be oestrogenic. However, the most potent carcinogens have only weakly oestrogenic properties and enormous dosages of oestrogenic hormones are required to induce

malignant growth. Therapeutic quantities of these hormones are extremely unlikely to give rise to such changes. The underlying law governing the power of these related substances to influence epithelial proliferation and the oestrus cycle must be disclosed before their shared activity can be explained.

Still another naturally occurring body constituent, acetyl choline, was reported by Franks and Hall (1938) to have produced osteosarcoma in animals following repeated subcutaneous injection of large doses. This claim has not yet been confirmed but it conjures up very interesting possibilities because of the specialized function of acetyl choline.

Detailed exploration of the entire field of inter-cellular and intra-cellular body chemistry must eventually bring to light the factors influencing normal and malignant growth expression. Great advances have been made in the past five years; much remains to be learned.

THE INFLUENCE OF INHERITANCE

A fact long disputed, but now generally accepted, is that certain constitutional factors predispose some animals to form cancer and predispose others against its formation. These constitutional factors, which are transmitted from one generation to another, have been extensively studied in laboratory animals. Close inbreeding has produced many pure strains, especially in mice and rats, and has permitted controlled investigation of numerous inherited characteristics. By thus reducing the genetic variability it has become possible to determine the effects of other influences such as age, sex, and diet.

In certain cases the Mendelian laws of dominance and recessiveness have been demonstrated but these phenomena are by no means universally applicable to neoplasms. Slye (1937) maintains that malignancy is transmitted as a localized recessive factor, each type of malignancy (carcinoma, sarcoma, leukemia) being a unit character and capable of suppression by a dominant. Breast cancer, for instance, requires two recessive characters for expression, one for malignancy and one for location according to her calculations. Little (1933), Murray (1935) and Bittner (1937) have, on the other hand, presented convincing evidence that breast cancer in mice is not dependent on genetic influences. While most non-mammary tumors seem to be distributed in essentially the same way as are the chromosomes, mammary tumors do not follow this pattern.

In strains susceptible to mammary adenocarcinoma the potentiality for neoplastic growth varies from 50 to 100 per cent. The incidence in virgin females, in the majority of these strains, is considerably lower than in breeding females, indicating that lactation may have an irritative effect. Forced breeding, with no opportunity to nurse the young, also appears to raise the tumor incidence by chronic irritation (Bagg, 1937). The practice is, therefore, to consider the incidence in breeding females as characteristic of the strain.

When females from an established high-tumor stock were crossed with males from a low-tumor stock a higher than expected percentage of the female progeny developed mammary tumors (Little, 1933). The reciprocal cross of low-tumor females with high-tumor males yielded a significantly low percentage of mammary cancers. These results indicated a strong maternal influence located outside of the chromosomes. At first the cytoplasm of the egg cell was considered to be the source of this extra-chromosomal element. Bittner (1937), however, revealed the source of at least one agent not located in the egg cell. He used low-tumor stock, lactating females to nurse young mice separated from their high-tumor stock mothers. Of these fostered mice only 7.4 per cent of the females developed tumors in contradistinction to 83.6 per cent of their sisters and parent stock. Reversing the arrangement, by having high-tumor stock females nurse the young of low-tumor stock mothers, he found the cancer incidence was raised almost to the level of the foster mothers. (By eliminating any chances of the young nursing their own mothers for the first few hours of life he expects to reduce the 7 per cent incidence of tumors to zero.) The average tumor age remained the same in all cases and, as the mice which did not develop tumors lived three to four months longer than the others there was greater opportunity for expression of the cancer tendency.

Bittner (1939) has extended his investigations to include the effects of foster nursing on the hybrid stock in which the extra-chromosomal influences were first noted. Further confirmation of the findings in the genetically homogeneous stocks was obtained. Mice from the high-tumor stock females—low-tumor stock males, when nursed by low-tumor stock females, showed a drop in tumor incidence as compared with sister mice raised by their own high-tumor stock mothers. Potentially high-tumor mice, therefore, transmit a "breast-cancer producing influence" in their milk. The nature of this influence, whether chemical, virus or hormonal, has yet to be determined.

MacDowell (1936) found that the incidence of leukemia in mice was significantly higher when the mother carried the leukemic heredity. The source of the leukemia-producing influence has not yet been reported. Lynch (1937) investigated the possibility of extra-chromosomal influence on inheritance of lung cancers. She found that both spontaneous and induced lung tumors were subject to genetic control but suggested that this control might be upset by external agents of great potency.

Very little is known of the comparative importance of extrinsic and intrinsic factors in most tumors. Heredity and environment do not appear to have the same relative effects on all types of tumors. A strong hereditary influence is recognized in human beings in whom retinal glioma or intestinal polyposis occur, while some other neoplasia, as lip cancer, appear to depend more on environmental factors. In special industries and in association with certain diseases causal connections

have been traced between the inciting factor and the neoplastic reaction in human beings. Where certain individuals display a resistance to a powerful inciting agent we must conclude that inherited characteristics are operating in their defence.

Certain principles, which are characteristic of all mammals, have been established by the study of cancer genetics in pure strains:

1. Constitutional differences in susceptibility are inherited.
2. Susceptibility is specific for organs.
3. External agents can induce neoplastic changes.
4. In some sites the response to the agent is controlled by the genetic constitution of the individual.

Genetic factors exert a considerable influence on the transplantability of tumors. Some tumors require only one genetic factor to permit their propagation while others require as many as five to seven. Tumors requiring few factors can be readily transplanted in nearly all strains of the species in which they arose; those tumors which require multiple genetic factors can only grow in the strains which carry all or most of the necessary factors. In some cases it has been possible to adapt the tumors to grow in strains which would not at first harbour them.

While transplantability within the original species can be carried on indefinitely, almost all attempts to transfer tumors from mice to rats, cats to dogs and man to lower forms, have failed. Under rigid control some mammalian tumors have been grown in developing chick embryos and a mouse sarcoma has been carried for several generations by transplanting it into new-born rats. Apart from these two instances heteroplastic transfer of mammalian tissue has been considered impossible and useless for experimental purposes. The success of Greene and Saxton (1938) in propagating rabbit adenocarcinoma in guinea pigs and human breast cancer in rabbits has changed this attitude. By their method human cancer can be indefinitely cultivated in the anterior chamber of the eye of the rabbit. This new technique may be applied to a wide range of physiological and pathological problems and opens a whole new field of investigation into human cancer.

THE BASIS OF MALIGNANT CHANGE

An apparently unrestrained capacity for proliferation is the outstanding biological characteristic of malignant tumors. A normal cell is transformed into a malignant cell by some action from without but once the transformation has occurred the external stimulus is no longer necessary for the maintenance of the malignant character. Cancer cells are permanently altered, as evidenced by their abnormal intensity of growth and their ability to retain indefinitely those characteristics which first distinguished them from surrounding normal cells.

Malignant change can be induced by a wide variety of extrinsic agents, such as hormones, pure chemicals, X-rays and parasites. These diverse agents seem to initiate a process of mutation within the normal cell. Actually, visible distortion of the chromosomes from heavy

X-radiation has been demonstrated in plants, with a resultant change in the characters of the affected cells. The other carcinogenic substances, however, appear to work more indirectly on the chemistry of the cells, probably producing an ultimate chromosomal upset. Their effects are conditioned by intrinsic factors of the organism which may be termed "susceptibility." On this premise it is easy to explain why different pure strain animals react differently to the same stimuli. The threshold of mutation may be lower in "susceptible" strains, or lower in certain organs of such strains, so that a change in external or internal irritants may induce mutations in these organs.

In support of the mutation theory of cancer origin is the fact that intermediary phases between normalcy and malignancy have been difficult to demonstrate in cells. Certain precancerous changes can be pointed out by the pathologist but the stage whereat the cell actually assumes malignant characteristics is still unknown. Various attempts have been made to induce normal cells in tissue culture to take on malignant properties by exposure to carcinogenic agents. When the transformation occurred, as it did very infrequently, it was so sudden that the intermediate stages were obscured. Lower animals have been experimented upon in further attempts to clarify the problem but, while some growth stimulation of bacteria (Goldstein, 1937), Planaria (Owen, 1938) and Obelia (Hammett and Reimann, 1935) was evident after exposure to carcinogens, no new information was revealed.

In tissue cultures those chemicals which are very potent in producing tumor responses *in vivo* appear to retard the growth of normal fibroblasts and even exhibit toxic properties. Consequently Reimann (1938) has stated that "stimulation of cell proliferation alone does not lead to neoplasia." A new approach to this phenomenon was found by Murphy (1937) when he discovered the presence of inhibiting substances in extracts of placenta and embryo skin. The intraperitoneal injection of these extracts into animals with spontaneous mammary cancer caused the arrest of growth in 70 per cent and actual regression in 22 per cent of the tumors. More recently, there has also been isolated a potent inhibiting fraction from the prelactating mammary tissue of the cow and rabbit. Some chemicals have been tested for inhibition of tumor growth and significant results have been obtained with heptyl aldehyde (the active principle of Wintergreen), with colchicine and with essential amino acids. These substances may have similar effects to the inhibitors of unknown chemical nature, discovered by Murphy, in retarding mitosis or other cell functions.

Murphy (1939) postulates that normal tissue growth is the result of a balance between stimulating and inhibiting factors but that the removal of one or more inhibitors permits neoplastic proliferation. These stimulators and inhibitors are possibly chemical in nature and their role in the conversion of cells from normal to malignant behaviour is probably based on profound metabolic changes.

* * *

The aim of cancer research is, of course, the discovery of the cause of cancer. The successful treatment of a disease may be planned without knowledge of its cause but it is essential that the cause be known before preventive measures can be devised. So many approaches to the problem have been disclosed by research work in the past few years that a survey of the entire field leads only to confusion. In his 1938 report on the British Empire Cancer Campaign, Sir Alfred Webb-Johnson adequately describes the present situation: "The truth must be demonstrated by some rare genius with a faculty for seeing the hidden relations between the various phenomena." Since normal and malignant cells have many characteristics in common, it is conceivable that when the laws of typical growth are discovered the atypical or cancerous growth will also yield up its secret.

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The Significance of Harvey's Contribution to Physiology and Medicine*

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HIPPOCRATES taught that the functioning of the organism was the proper subject of the physician's study. Many centuries afterward, William Harvey, by his studies of the circulation of the blood, was the first to show that vital phenomena are related to the operations of definite organs. Harvey followed the trail opened up by Vesalius and other early anatomists until it led to a great physiological truth. His course was the course of every true scientist since his day, that is, reasoning based upon experiment and observation.

Sir Michael Foster chose to regard Harvey not as the "Discoverer of the Circulation" but rather as "he who was the first to *demonstrate* the circulation of the blood." Harvey's methods of investigation were those which may be called strictly physiological methods and Fulton has remarked that "the introduction of the experimental method into physiological science, for which Harvey was responsible, was no less significant than the discovery of the circulation."

Judged by modern standards of medical research, his technique might not rate very highly, but viewed in the light of the learning of his day it was remarkable. We must not forget that Harvey had no instruments of precision to aid him in his experiments. The science of physics was in its infancy and there were not any perfect physical conceptions. There was no chemistry except that of the ancients and there were no certain biological principles to which he could appeal. There was, however, plenty of philosophizing about Nature. There were superstitions and a tenacious adherence to the doctrines of Galen. It was under such circumstances and in the face of much criticism that Harvey had the courage to record precisely, logically, modestly, what he saw and what he thought concerning the movements of the heart and the blood. His work has not been rendered obsolete by subsequent knowledge. William Harvey, therefore, was the effective founder of modern physiology without which there could be no Science of Medicine.

In our day, it is inconceivable that an investigator, having made original observations of the importance of those of Harvey, should wait twelve years before publishing his results. Perhaps some modern researchers might be guided by Harvey's reticence in this regard. It is true there was no incentive for Harvey to rush into print. Competition in his particular field of research was not active and the opportunities

*Read at the Twentieth Annual Banquet of the Harvey Club, London, Ontario, February 28th, 1939.

for the speedy publication of experimental observations were not what they are today. ("Publicationitis" assumed epidemic proportions only in recent years.) Furthermore, his ideas were not generally accepted. In common with certain reports of research activities subsequently, "his views pleased some, displeased others." As a matter of fact, his announcement regarding the circulation was greeted in some quarters with scepticism and derision and he was subjected to scorn for daring to question the philosophical authority of Galen and his disciples. Although Harvey suffered materially, his demonstration of the circulation of the blood afforded the death-blow to the Galenic physiology, including the "spirits," and to the old humoral pathology, an achievement sufficient in itself to place him among the Immortals.

Following the publication in 1628, in a foreign country, of Harvey's views on the circulation of the blood, the growth of physiology was slow and it did not have immediately any great effect on medical practice. Fresh impetus to physiological research was supplied by certain other scientific developments, namely, the birth of physics during the early part of the 17th century followed somewhat later by the evolution of rational chemistry from a mystic alchemy. In addition, there came to the aid of those who were inquiring into the problems of life the microscope, which opened up an entirely new world of Nature. One hundred years ago (1839) Theodor Schwann enunciated the "cellular theory" as applied to animal structures and at the same time Liebig introduced chemistry to physiology. Such advances marked an epoch so aptly described by Daly, "when the men interested in the pure sciences wholeheartedly joined hands with those in Medicine, thereby inaugurating a liaison, the importance of which can only be estimated in the light of our present knowledge."

While Harvey grasped the truth of the circulation, he was never able to follow it throughout, for he could not see the capillary vessels. It remained for another to find the missing link. Three years after Harvey's death, Malpighi demonstrated the existence of the connecting channels between the terminal branches of the arteries and the smallest tributaries of the veins.

Sir Michael Foster wrote that "all the deeper problems of physiology turn on the mutual action of the tissues and the blood, as the stream of the latter sweeps among the elements of the former. In science no man's results are wholly his own; like other living things they come from something which lived before. Harvey showed that the blood did sweep through the tissues; Malpighi showed how the blood swept through them." Schwann showed what the normal tissues were and invented the word *metabolism*. Virchow applied the cell theory to diseased tissues. "Thus the way was opened for those inquiries into the ways in which the blood acts on the tissues and the tissues act on the blood, inquiries the results of which are the pride of modern times and the hope of times to come."

Harvey was the first of a notable group of medical men in whom the urge to discover new truths took them away from the mere routine of practice into the realm of research and whose careers have brought "physiology and medicine into that close and special relation indicated by the common etymology of the words 'physician' and 'physiology'." A compilation of the names of those who have been both "clinician" and "scientist" would include: Marcello Malpighi, Hermann Boerhaave, Richard Lower, Jean Conrad Peyer, von Brunner, James Black, William Cruikshank, William Beaumont, Thomas Willis, Francis Glisson, Alexander Stewart, Charles Bell, Robert Whytt, Marshall Hall, Brown-Sequard, David Ferrier and, in our own time, Leonard Rowntree, Sir Frederick Banting, Harvey Cushing and Sir Thomas Lewis. The last-named, like Harvey a student of cardiovascular phenomena, probably more than any other individual by his work and teaching has bridged the gap between the laboratory and the clinic.

The true significance of Harvey's contribution to physiology and medicine has been stated by Singer in the following words: "The knowledge of the circulation of the blood has been the basis of the whole of modern physiology and with it the whole of modern rational medicine. The blood is a carrier, always going round and round on the same beat. What it carries and why, how and where it takes up its loads, and how, where and why it parts with them, these are the questions the answering of which has been the main task of physiology in the centuries that have followed. As each of the questions has obtained a more and more rational answer, so clinical medicine has always made a step forward and has come to approach more nearly to a true science. Thus it is that the work of Harvey lies at the back of almost every important medical advance."

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In the nineteenth century, Kalesnikoff, a Russian shoemaker, disguised himself as a doctor and rapidly rose to the office of chief surgeon at the Kieff Hospital. He performed 600 major operations before his imposture was uncovered.

* * *

In remote sections of India patients contemplating an operation demand the burning of incense in the operating room — otherwise devils might enter the body through the opening.—FACT DIGEST.

On the Diagnosis of Pulmonary Tuberculosis

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WHEN one attempts to add something to the overburdened literature concerning this subject, it is done with apology. However, it is felt that there are certain changes which have occurred in our knowledge of the nature of pulmonary tuberculosis during the past two or three decades which are of sufficient importance to command the attention of the general practitioner, the man upon whose shoulders rests the task of decreasing one of the chief causes of death among our youth.

Since the advent of the science of Roentgenology and the employment of routine chest plates under certain circumstances, the earliest lesion which has been observed is the so-called Assmann infiltrate. Radiographs indicative of the lesion are shown in figures 1 and 2.

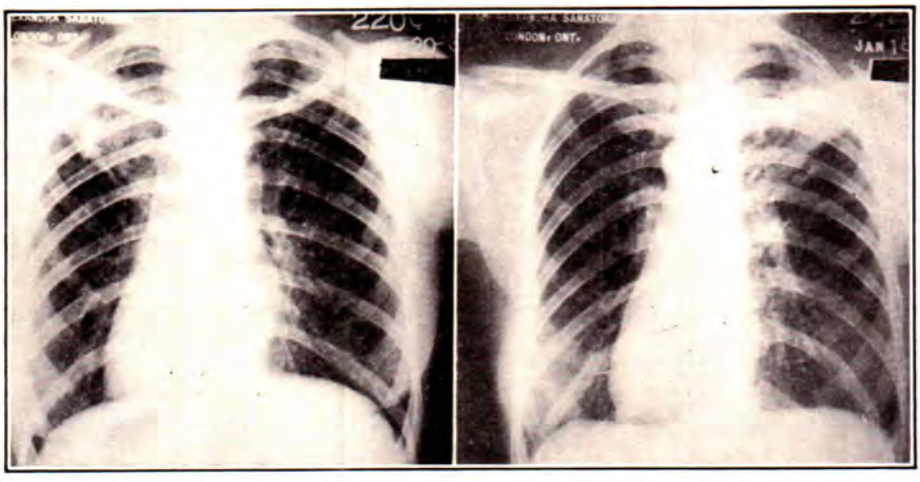

Figure 1 Figure 2

These two radiographs indicate the characteristics of a somewhat advanced Assmann infiltrate. Note that in either case the lesion is located chiefly in the axillary half of the first intercostal space and that the spread of the disease has occurred from that point.

The radiographic appearance of this lesion is that of a soft, fluffy opacity approximately one to two cm. in diameter. It may be located anywhere in the pulmonary parenchyma, the site usually being in the axillary half of the clavicular region. In some cases, the characters of

this small area have been observed to change rapidly. Exceptionally, it may completely resolve. Conversely, the infection may advance rapidly to involve the upper lung in an acute tuberculous process, frequently accompanied by cavitation. Few pathological findings have been described. Those which have been reported correspond somewhat to those of the primary infection if the lesion is exudative in type. Certain characteristics of the secondary invasion are retained.

The history elicited from patients suffering from this process is *extremely* variable. There may be scarcely any alteration from the usual state of health. The majority tell of *fatigue* which is most noticeable at the end of the day; that is, they are more fatigued than usual at the end of a day's work. Upon awaking, they feel miserable and at this time may suffer from coughing spasms. *Blood-streaked sputum* or *frank haemoptysis* may now appear but its absence is not indicative. *Pleurisy* may have been present previously or assert itself now for the first time. As the condition advances, low-grade mid-afternoon *pyrexia*, accompanied by the characteristic flushed face supervenes. All early symptoms become progressively aggravated. A past history frequently reveals an "influenzal attack" shortly before the onset of the present illness. Excessive perspiration is an additional manifestation of weakness.

This symptom-disease complex is surely of a different nature than we formerly understood. As the disease advances it resembles the chronic type of pulmonary tuberculosis. With such cases, the presence of the low-grade chronic infection is known to cause a mild degree of secondary anaemia. This, coupled with the weakness induced by reduced exercise, brings about another train of symptoms characteristic of the chronic apical tuberculosis which our texts describe. Earlier diagnosis has allowed us to recognize certain symptoms which have previously passed unnoticed. However, this fact does not appear to explain the entire problem. It is our opinion that certain cases of pulmonary tuberculosis, such as we see today, represent a different type of disease than was recognized several years ago.

In the first place, it is a conceded fact that in this country, particularly in Ontario, the incidence of reactors to the intracutaneous injection of old tuberculin among youths and young adults has materially dropped. This reassuring fact is conceivably explained by the vigorous public health measures which have been so prominent during the past two or three decades. As a result, the cases of so-called primary or childhood infection are becoming steadily decreased. In other words, we must be encountering a group of young adults who are suffering from their primary or initial infection. We believe that it is this group who present the symptom-disease complex described above. This is confirmed by Rich and McMurdoch's enlightening work on allergy and immunity with respect to tuberculosis. They have shown that the primary infection, when it affects the adult, is in many respects similar

in nature to secondary infection. The infecting dose, according to their observations, is the single factor which determines whether the disease produced will have "primary" or "secondary infection" characteristics. On the other hand, others maintain that the uniformly high upper lobe localization and the earliness of cavity formation are clearly reinfection characteristics.

One wonders, since primary infection in childhood is usually a benign process, why it assumes a more serious nature when it affects the adult. It is an accepted fact that the chief known line of defense that the body can mobilize against tuberculosis lies in the lymphatic system of vessels and glands. We know that in the child the lymphatic system is abundant, the pulmonary network being no exception. As age advances, the lymphoid tissue throughout the body regresses, ultimately becoming atrophic. Further, when one considers the amount of pulmonary lymphoid tissue damaged from the effects of anthracosis as age progresses, it is not difficult to understand that the chief line of defense has been rendered less efficient. Thus the invading tubercle bacilli, so to speak, are left without foe and destruction supervenes. On the other hand, it may be possible that the child's open lymphatic system favors spread of the disease, whereas the adult's relatively closed pulmonary lymphatic system tends to localize it.

DIAGNOSIS

There remains little to be said regarding this problem. The chief difficulties which hinder early recognition may be summed up as: Failure to recognize the condition in the early stages because of silence of the disease and, therefore, when treatment is of most value; lack of co-operation of the patient; the high cost of diagnostic procedures.

Recognition of the condition is admittedly difficult during the early days of the disease. As a result, diagnosis has been largely turned over to chest specialists who operate free clinics in regional zones. Since the physician refers these cases, it is obvious that he must possess a reasonable degree of accuracy in the evaluation of symptoms which point to the chest.

A history of contact with a case of pulmonary tuberculosis is important circumstantial evidence. Persons with such a history must be subjected to a periodic chest examination until a definite conclusion is reached. The number of cases found among children under fifteen, examined because of contact or symptoms, has been found to be almost negligible. In case-finding programs, greater emphasis must be placed upon securing the examination of adult contacts. Occasionally one chest plate alone is valueless. Although it is our most precise instrument for the recognition of the condition, it is only an aid to diagnosis and must always be regarded as such. No radiologist is prepared to give a positive diagnosis from a doubtful shadow with no further information. Moreover, there are certain indefinite shadows which require serial

studies before a definite opinion can be given. We often expect a roentgenogram to make the diagnosis for us after we have failed to do so on clinical grounds.

A history suggestive of the condition in the absence of contact likewise must be thoroughly investigated. One important point to bear in mind is that the use of the stethoscope with regard to early disease of this type must be, of necessity, discarded. True, it is of value, but negative physical findings in a suspicious case should never be allowed to deceive one. The discovery of respiratory lag is the best single sign of a pulmonary tuberculous process, either recent or old.

Haemoptysis and *pleurisy* are to be regarded as manifestations of pulmonary tuberculosis until definitely proven otherwise. A glaring example is the case of a young wife with a history of haemoptysis on two occasions, each occurring after swimming. Other symptoms were not prominent. A physician informed her that a small vessel in her throat had ruptured and so the case was dismissed. On admission to Queen Alexandra Sanatorium, radiological examination revealed the presence of a large cavity near a lung hilus. Pneumothorax was attempted on several occasions without success, due to the presence of adhesions between the parietal and visceral pleurae.

The *red blood cell sedimentation index*, and *red blood cell sedimentation time*, although by no means specific for pulmonary tuberculous, is a far more accurate index of the activity of the disease than either the temperature chart or the white blood cell count. Early cases will usually show a red blood cell sedimentation index between 10-25 mm. in the first hour as determined by Cutler's vein method. This procedure should be performed on all suspected cases even prior to the far more costly X-ray examination.

Lack of co-operation is a factor which, in most cases, is due to a horror of the disease. Here the physician must exert his whole-hearted persuasiveness in order to dispel such fears. Sanatorium life is pleasant; the majority of inmates are contented.

The high cost of diagnostic procedures is a factor which has been met to a large extent. The availability of free clinics throughout the country has done much. However, under our present system, it is the middle-class individuals who must absorb a great proportion of the expenses incurred, in addition to paying for their own. Surely this one fact is sufficient evidence to direct attention to the serious need for some type of social insurance system.

Finally, routine examination of the chests of all young adults in every walk of life is perhaps an ideal which will take years to reach. However, there are various institutions, particularly nursing schools, which have shown us the value of this procedure. The method consists of tuberculin-testing all entrants and the subjection of positive reactors to X-ray examination. One has only to see cases identified in this manner, which later yield almost universally favorable results, to be

convinced that it is the only method of eliminating this terrible scourge, according to our present knowledge.

SUMMARY

1. A new form of pulmonary tuberculosis has been described. It is not inferred that it is a new disease. Modern diagnostic procedures have allowed us to recognize the early manifestations of the onset of the condition.

2. It is difficult, however, to state whether we are seeing tuberculosis earlier than before, or whether this disease is the result of a so-called primary infection in the adult.

3. The routine method of diagnosis is described.

* * * *

The author is indebted to P. M. Andrus, M.D., F.R.C.P.(C). for reading and criticising this paper.

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MENTAL EFFICIENCY

People think better lying down. Further than that, the chap who sits with his feet up on the desk is doing a good job of thinking for the boss. Upright evolution was a major mistake in human history because the erect posture deprives the brain of blood. These are some of the discoveries of Dr. Donald Anderson Laird, psychologist of Colgate University, in whose laboratory the role of guinea pigs is played by the human being and his mental processes.

Dr. Laird's work is described by G. Edward Pendray in Today magazine. The writer gives the psychologist credit for another great discovery, namely that nobody sleeps "like a log." The ordinary sleeper squirms and turns ten to twenty times a night, which is something a log cannot do. Six hours of sleep are enough for anybody. That is another discovery of the Colgate professor, who adds the other two hours on each day's sleeping allowance are sheer luxury, amounting to waste of ninety-one eight-hour days a year.

The Patient With a Headache

By L. D. WILCOX, M.D., F.R.C.P.(C)
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HEAD pain is a common experience to most of us, although in the majority of instances it does not have a serious significance. However, in some patients it comprises the chief complaint of a serious condition, and so calls forth our best diagnostic and therapeutic efforts. The purpose of this paper is to outline briefly some of the common causes of headache, and an approach to patients who complain of chronic or recurring headache. The treatment of the condition is usually fairly definite once the cause has been established, except perhaps in the migraine type of headache. Therefore, a short account of this malady along with its now very effective therapy will be included.

COMMON CAUSES OF HEAD PAIN

Brain: Concussion, tumor, abscess, diffuse inflammation, hydrocephalus, vascular changes.

Meninges: Infections, adhesions, haemorrhages, neoplasms.

Skull: Tumor, suppurative states in the bone or sinuses, dental conditions, metabolic diseases of bone.

Disturbances of the Organs of Special Sense: Eyes, ears, nose.

Toxic Causes: Carbon monoxide, alcohol, tobacco, drugs such as luminal, opium, salicylates, acetanilide, constipation, uraemia, cholaemia.

Functional Conditions: High or low blood pressure, mental or emotional stresses, migraine.

THE INVESTIGATION OF THE PATIENT

History of the Pain: Its time of onset, duration, type, location, precipitating factors, severity (whether or not it prevents sleep, work or play), measures that give relief, and associated symptoms should all be noted.

Family History: This is positive in three out of four migraine patients. The presence of vascular disease or of psycho-neurotic trends in other members of the family should be ascertained.

Past History: This covers the general health of the patient, infections, head injuries, and operations, especially those involving the nose or sinuses.

Functional Inquiry: This should touch on all symptoms referable to the eyes, ears, nose, sinuses, teeth, gastro-intestinal system, with particular emphasis on the functioning of the stomach and colon, cardio-vascular system, genito-urinary tract, skeletal structures, and the central nervous system. The patient's performance at work or play deserves attention at this point, as do his environment, the drugs he uses, sleep, and weight.

PHYSICAL EXAMINATION

General Appearance: This often gives one a real clue as in the case of the acromegalic, the anxiety neurotic, and, to the experienced diagnostician, the patient with a brain tumor.

Skull: The contour, findings on palpation, percussion, and auscultation are important.

Eyes: External ocular muscles, visual fields, tension, fundi, refraction (short-sighted people do not have headaches while those who are far-sighted may have intense ones after eye work if the error has not been corrected with suitable glasses).

Nose: Obstructions are looked for.

Sinuses: Tenderness, pain experienced on stooping, and clouding on transillumination.

Ears: Hearing acuity, presence or absence of a discharge must be investigated.

Chest: It is a common site of the primary focus in tuberculous meningitis, brain abscess, and brain tumor.

Circulation: The heart, the condition of the arteries, and the blood pressure are recorded.

Meningeal Signs: A stiff neck and a Kernig are suggestive.

NEUROLOGICAL EXAMINATION

Speech, gait, muscular power, cranial nerves, reflexes, sensory findings, cerebellar signs are investigated.

GENERAL SURVEY

The neck, breasts, chest (X-ray), skin (moles and fibromata), kidney and adrenal areas, and the prostate are examined with a view to detecting primary sites of neoplasms that frequently metastasize to the head region.

SPECIAL STUDIES

Urine: It is examined for albumen, sugar, and sediment.

Blood: A white cell count and sedimentation rate will exclude most active infections. The hemoglobin estimation will point to polycythemia or anaemia that may have gone unrecognized. The blood N.P.N. and Wassermann should be done routinely.

Lumbar Puncture: When all other findings are negative, and a careful examination of the fundi shows no evidence of increased intracranial pressure, this procedure is indicated. It is of greatest aid in diffuse inflammations of the brain or meninges, whereas in tumor or abscess it is rarely helpful and may even carry a serious risk. When doing a spinal tap one should always be equipped with a simple water manometer with which the cerebro-spinal pressure can be measured. The old "drop method" and the mercury manometer are both grossly inaccurate. The fluid should be cultured, and then studied for cells, globulin, chlorides, and serological abnormalities.

X-Rays of the Skull: These should be obtained whenever possible;

a single or stereoscopic lateral view often gives much information as in the following conditions: Enlargement of the sella turcica, thinning of the cranial vault by the raised intracranial pressure of tumor, dislocation of a calcified pineal gland, diseases of the skull itself—as with metastatic lesions or metabolic disturbances such as hyperostosis frontalis (a diffuse or localized thickening of the skull that is usually associated with severe headache), and brain tumors that have become calcified.

Air Injection: This may be done by the lumbar route when a visualization of the sub-arachnoid space (and the ventricles occasionally) is desired. The largest field of usefulness for this technique is in the post-traumatic group of cases. It is not correct to use it in patients who have increased intracranial pressure, and it is not worth doing unless one has the facilities for very accurate X-ray work. Of much greater value is the ventriculogram, which is the method of choice for tumor patients. Cerebrospinal fluid is withdrawn and replaced by air after a brain needle has been introduced into the posterior horn of one or other lateral ventricle through a small trephine opening. It is a dangerous procedure and not to be contemplated unless a neuro-surgical unit ready for immediate operation is at hand.

MIGRAINE

This disturbance is characterized by attacks of intense pain on one or both sides of the head and is associated usually with nausea and vomiting, visual symptoms, and sympathetic or psychic phenomena. Great variations occur in different episodes in the same individual. The one constant feature is an entire relief from pain between attacks.

Mental or physical fatigue, emotional upsets, or menstruation may act as precipitating factors of the headache. The frequency may vary from one or more attacks a week to several in a year, and the economic loss will often therefore be marked. A foreboding or "aura" is common as a feeling of tension, anxiety, fatigue, or abnormal weakness. The pain may appear at any time of the day or night.

The headache often begins behind the eyes; it may involve the frontal, temporal, or vertex areas and in many instances radiates back to the occiput and even down to the neck and into the shoulders. Pain over one side of the head is encountered in perhaps one-half the number of the cases. It increases gradually in intensity and may be described as dull, boring, pressing, throbbing, hammering, or vise-like.

Vomiting tends to occur at the height of the attack so that many believe it heralds the end of the headache. Actually the duration of the pain is measured in hours or occasionally in days. The condition is rare after the age of 45. True migraine is not often helped by codeine and aspirin mixtures or by pyramidon.

Before resorting to special drugs one should always attend to the

physical, mental, or emotional factors that may militate against successful treatment if not corrected. The specific treatment for migraine is ergotamine tartrate put up under the trade name of Gynergen. It can be used by mouth, subcutaneously, or intravenously.

Symptoms which accompany its use are nausea and vomiting, weakness of the legs, stiff joints, constriction in the throat, heaviness in the chest, and sometimes tingling in the toes; the pulse tends to fall and the blood pressure may rise. It is therefore unwise to use it in the face of heart disease, hypertension, or pregnancy.

Gynergen gives rise to a fullness in the head, loss of the headache, and a feeling of healthy fatigue within one-half hour of its use by vein; within two hours after hypodermic injection; and within perhaps four hours of oral administration. Severe headaches often fail to respond to the drug by mouth.

It is best to give 0.5 cc. (0.25 mgm.) subcutaneously and a similar amount by vein as early in the attack as possible; or the 1 cc. may be given subcutaneously with a slightly greater degree of safety.

Success will follow the use of the drug by vein or subcutaneously in more than 90 per cent of cases if it is used in adequate dosage, and it will continue to relieve the headaches even after 100 attacks. It is well to remember that variations in the severity of the headache are found in any one individual. When the patient feels he is "in for a bad one" the maximum dose (1 cc.) should be given; otherwise 0.5 cc. subcutaneously will often prove sufficient. If the pain has attained a peak before treatment, a full dose should be given at once. As a rule, the earlier the drug is given the smaller the dose required. If the headache does recur, a second injection may be given safely and successfully. Such repeats are often needed if the first treatment has not been given early in the attack.

The dose of Gynergen by mouth is 1 to 4 mgms. at the beginning of an attack. It will give good results in more than 60 per cent of the cases. Its use as a prophylactic measure is inadvisable.

No patient should be given the drug unless he is absolutely quiet at bed rest. A few patients who are distressed by much nausea and vomiting after drug treatment may escape these symptoms if given atropine sulphate gr. $\frac{1}{100}$ by hypodermic injection after the Gynergen has been given.

Gynergen probably acts by constricting the blood vessels in the scalp or meninges. It is safe to add that its use marks the greatest gain that has ever been achieved for migraine sufferers.

Among the awards offered at a Los Angeles charity ball held last year was a free operation.

Drug Allergy

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CASE REPORTS

CASE 1—A woman in her third confinement was given an injection of ergot extract at the stage at which this is usually done. There was nothing abnormal about the patient nor the labour, and up to the time of the injection everything was going along normally. Within a few minutes of the injection she went into a state of collapse, became pulseless and unconscious. It looked as though she were going to die within a few minutes. For several hours she remained in this state of collapse (a period which must have seemed like weeks to her physician).

Gradually her pulse became apparent, consciousness returned and she became normal again. Later, it was learned that a somewhat similar, though not so severe, reaction had occurred during her previous pregnancy, when she had been attended by a different doctor but had been given a similar injection

CASE 2—A man was admitted to hospital for removal of nasal polyps and for investigation of his chronic bronchitis and asthma. Among other points in the history, he told the interne that he could not take aspirin because it gave him violent asthma.

On account of the poliomyelitis epidemic which occurred at this time all non-urgent operations were postponed, so the man was sent home and told to return in two or three months to have the polyps removed.

He was re-admitted several weeks later on account of an acute bronchitis, or possibly broncho-pneumonia. He was sick when admitted after supper one evening, but his general condition, pulse rate, etc., did not suggest that he was seriously ill.

The interne had left the service since his first admission and a new interne was in charge. The patient complained of soreness and aching in the chest muscles and an aspirin compound tablet was prescribed.

One hour and a half later the man was dead.

DISCUSSION

Anyone who administers drugs for any purpose in any disease is not only liable but bound to run into the problem of drug allergy from time to time. Not all allergic reactions to drugs are as spectacular as those mentioned in the above two case reports. They may be quite mild, as well as fatal.

We have all known patients who have said, "I can't take aspirin (or ipecac, or arsenic, or some other drug)." And we all know patients who have brought back a bottle of medicine, or a prescription, after taking one or two doses and said, "I can't take this, Doctor; there's something about it which doesn't seem to agree with me at all." Such cases are most likely instances of allergy to drugs. When a drug is prescribed in regular sized doses there are three different responses possible. First,

and most likely, we will obtain the usual expected therapeutic result. Secondly, occasionally we get the same result but in an abnormally exaggerated degree. For example, a usual dose of quinine may cause buzzing in the ears, deafness or nausea. These are the usual toxic effects of large doses. In these cases of *drug intolerance* we can get the proper degree of therapeutic response with a fraction of the usual dose; or we can get the ordinary toxic symptoms with the regular dose. Thirdly, also occasionally, we get an unusual and often spectacular reaction. For instance, one aspirin tablet may be followed suddenly by severe bronchial constriction, collapse, and perhaps death. These are true cases of *drug allergy or idiosyncrasy*.

A table is appended, giving in compact form the main allergic reactions one may expect from the more commonly used drugs.

Drugs are given and taken so frequently these days that, even if allergy to drugs occurs in only a minute percentage of patients, the actual number of these people is quite large and they are frequently encountered. If we realize that between 50 and 60 per cent of all people are potentially allergic to some drug, we are impressed with the fact that we must keep the possibility of drug allergy constantly in the back of our heads—and not too far back in our heads, either.

To skin test for drug sensitivity is not possible, except in the case of sera (antitetanic, scarlet fever antitoxin, etc.) and glandular products (insulin, thyroid, pituitrin, etc.). Therefore we are forced to depend upon what the patient tells us regarding past experiences with drugs, or else upon observation of the actual effect of taking a small quantity of the drug. Aspirin can be tested by placing half a grain on the tongue and observing what happens.

If we discover that a certain patient is allergic to a certain drug, it is our duty to tell them the name of the drug, what sort of preparations it is likely to be found in, and explain the trouble they are bound to get into if they ever take it in the future.

If someone tells us that they cannot take a certain drug or prescription, let us not commit the unforgivable error of disbelieving him or, what is worse still, deliberately misleading him by saying that there is none of that drug in a prescription when we know there is. "What they don't know won't hurt them" may hold true in a number of circumstances but not in drug allergy, where "What they don't know *may* kill them."

DRUG	SYMPTOMS OF INTOLERANCE	ALLERGIC REACTIONS
Acetanilid	Nausea, vomiting, cyanosis, dullness, confusion.	Maculo-papular eruption, urticaria, edema, eczema, erythema-multiforme-like eruption.
Antipyrine	Catarrh, burning, swelling of mouth and throat.	Erythema - multiforme - like eruptions. Fixed or circumscribed, erythematous or bullous, polychromatic, pigmented eruptions, urticarial and purpuric lesions, edema of lips.

Aspirin	Disorders of hearing, dimness of vision, delirium, nausea, vomiting, diarrhea.	Angioneurotic edema, pruritus, urticarial and scarlatiniform eruptions, conjunctivitis with occular edema. Coryza. Asthma, Death.
Amidopyrine		Edema, Urticaria. Agranulocytosis (?).
Arsenic	Abdominal colic, nausea, vomiting, diarrhea, coryza, rhinitis, conjunctivitis, edema of lids; hepatitis with jaundice.	Scaly erythematous eruptions. Purely erythematous and morbilliform and dermatitis-exfoliativa-like eruption. Hyperpigmentation. Edema of extremities. Asthma.
Arsphenamines	Gastro-intestinal disturbance, colic, diarrhea, hepatitis with jaundice, encephalitis.	As above plus: eczema, purpuric eruptions. Fixed polychromatic, pigmented eruptions. Anaphylactoid symptoms. Herxheimer's reaction.
Barbituric acid derivatives	Stupor, coma, confusion, nausea, excessive thirst, cyanosis.	Edema. Urticaria. Fixed pigmentary eruptions.
Bismuth	Stomatitis, salivation, black gum-line. Nausea, vomiting, diarrhea.	Urticaria. Erythematous eruption. Bullous and purpuric lesions.
Bromides	Gastro-intestinal disturbance, nausea, vomiting, diarrhea. Incoördination, lack of concentration. Rhinitis, coryza.	Erythema-nodosum-like eruption. Acneform, furunculoid, and erysipelas-like eruptions. Ulcerating and vegetating eruption. Urticaria.
Belladonna	Excessive dryness of mouth and throat, unquenchable thirst and perverted sense of taste. Nausea and vomiting; vertigo. Dilatation of pupils, blurred or double vision. Palpitation. Physical, mental depression.	Urticaria; scaly erythematous eruptions; purely erythematous eruptions, and morbilliform and dermatitis-exfoliativa-like eruptions, hyperpigmentation edema of extremities. Asthma.
Copaiba and Cubeb	Gastro-intestinal disturbance.	Urticaria. Eczema. Erythema-nodosum-like eruptions.
Ergot	Convulsive seizures. Gangrenous symptoms.	Thrombocytopenic purpura.
Insulin	Uneasiness. nervousness, weakness, faintness, sweating, thirst, incoördination, unconsciousness.	Urticaria, asthma, ocular edema. Gastro-intestinal disturbance. Cramps, diarrhea.
Epinephrine	Tremor, nervousness, palpitation, precordial distress.	None.
Mercury	Stomatitis, metallic taste, salivation, colic, diarrhea, nausea, vomiting, blue gum-line.	Erythema, eczema, vesiculation, weeping, scaling, pruritus.
Opium, Codeine, Morphine	Contraction of pupils. Diarrhea and constipation, melancholia, dementia, headache, nausea, vomiting.	Erythema. Pruritus.
Phenobarbital	Gastro-intestinal disturbance. Diplopia, vertigo, speech disturbance, mental confusion, weakness, and incoördination.	Edema. Urticaria. Fixed pigmentary eruptions.
Phenolphthalein	Gastro-intestinal disturbance.	Urticaria. Erythema-multiforme-like eruptions. Fixed erythematous or bullous, polychromatic pigmented eruptions.
Pituitary extract		Urticaria, angioneurotic edema, respiratory difficulty. Pruritus.
Quinine	Nausea, vomiting, tinnitus, deafness, headache, disturbed vision, photophobia.	Eczema with erythema, vesiculation, weeping, scaling; thrombocytopœnic purpura.

The Modern Management of Pneumonia

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THE purpose of this paper is not, as the title may suggest, to give a complete outline of the management of pneumonia. Only a few recent advances in therapy are outlined and these pertain only to the pneumococcal pneumonias. Even in the year 1939, pneumonia still ranks third as the commonest cause of death. It is preceded only by cardiovascular diseases and cancer. Few of the prevalent acute conditions have such a high mortality or are so expensive to treat. When we consider that 25 per cent of our pneumonia patients die and that the majority of them come from our most productive age group, we then realize just how much skillful therapy is indicated in these cases.

In the past, the unhappy victim of lobar pneumonia perforce must cough, perspire, gasp for air for days on end until resolution or, at times, death ended his sufferings. Today, the picture changes. No longer is our conduct of the pneumonic patient one of watchful waiting. Pneumonia is a medical emergency. Active rational therapy carried out in the early stages of the disease will ameliorate and sometimes practically eliminate those toxic manifestations so distressing and injurious to the patient. Three factors contribute to this change: (1) Improvements in symptomatic treatment, (2) The introduction of chemical therapy, (3) The use of specific anti-sera.

SYMPTOMATIC TREATMENT

This aspect of the treatment, even in the face of changing therapy, still remains the basis and framework of pneumonic management.

(1) *General Measures:* Pneumonia is a contagious disease. As such, its victims should be isolated. In some centres, attendants wear masks when near the patient and follow the special technique associated with the treatment of communicable diseases. The room should be well ventilated, free of draughts and maintained at a temperature of 68° F. Good nursing is of prime importance.

(2) *Pain:* The pleuritic pain of pneumonia may be mild or severe, transitory or prolonged. To combat this, the opium derivatives, codeine and morphine, are of common use, the drug being suited to the degree of pain. Strapping the chest with adhesive is not advised since it is a barrier which the physical signs must penetrate to reach the physician's ear. A Scultetes binder is just as beneficial and does not hinder the physical examination. When the pain is very severe, the introduction of 200-300 cc. of air between the pleural surfaces with a pneumothorax apparatus gives complete and rapid relief.

(3) *Sleep:* The patient must sleep. A restless night caused by coughing, dyspnoea, and chest pain produces in the morning a much

more toxic and more miserable patient. A judicious use of sedatives will obviate this. Many observers will question the use of morphine on the ground that it increases the abdominal distension and is a depressant to the respiratory centre. They would favour the use of the barbiturates and codeine. Since we are able to produce such a rapid change for the better in the pneumonic patient, it is seldom necessary to use morphine for more than two to three nights. From then on, codeine and the barbiturates are quite adequate. But three factors keep the pneumonic patient awake, namely, cough, pain and dyspnoea. In the early acute case, no one drug can control these quite as well as morphine.

(4) *Cough:* This distressing symptom usually can be controlled with codeine either in the form of tablet or syrup. Seldom do we need the strong respiratory sedatives such as heroin or morphine. During the stage of resolution, expectorant cough mixtures are indicated. Here we have recourse to the various mixtures containing potassium iodide, ammonium chloride and ipecac listed in the B. P.

(5) *Diet:* For many years the diet in the early stages has been soft food with abundant high caloric fluids, the latter usually consisting of fruit juices. As the patient progressed, the diet was increased to light diet and then general. Some authors would prefer a full diet from the beginning, stating that the patient must have his full quota of calories to offset the demands of the body. At any rate, fluids are essential, up to 3,000 cc. *per diem* being the minimum.

(6) *The Bowels:* Abdominal distension must be treated actively and, if possible, prevented. It greatly embarrasses the patient's respiration. This distension is due to a paralytic ileus resulting from the generalized toxaemia present in pneumonia. Peristaltic stimulants such as castor oil, pituitrin or eserine may be given once or twice *per diem.* The use of castor oil may be questioned but it is an excellent small bowel stimulant. Small saline enemas every second day are advised. Along with the above, turpentine stupes and the rectal tube deserve a place.

(7) *Oxygen:* The rôle of oxygen in pneumonia is an important one. It decreases the cyanosis, relieves the dyspnoea, and lowers the temperature and pulse rate. The oxygen tent, especially the air-conditioned type, where there is a uniform inflow of oxygen carried in a circulating medium of ice-cooled air, is in general use. The one great advantage is that once placed in position little adjusting is needed. For days on end, the patient is assured of a uniform intake of oxygen. There is, however, the occasional patient who grows restless to the point of frenzy when placed in what he considers to be an oxygen "cage." Oxygen per nasal catheter serves well here and has the added feature of making the patient more accessible to treatment and physical examination. The rate of flow is easily adjusted and there is little waste. In England, nasal oxygen is much in vogue. They use a double nasal catheter in much the same manner as in intranasal anaesthesia. The saving in oxygen is apparently great.

(8) *The Heart:* Two conditions focus attention on the heart: auricular fibrillation which is uncommon and vasomotor collapse which is responsible for most of the deaths in pneumonia. The former can be well controlled with digitalis. The latter condition should be treated as a peripheral vascular collapse. Here we use adrenalin hydrochloride, coramine, camphor in oil, caffeine sodium benzoate, and intravenous fluids in small repeated doses.

CHEMOTHERAPY

In the past few years two drugs somewhat chemically allied have made their appearance in the treatment of pneumonia. The first was Sulphanilamide introduced in 1935 and the second Sulphanilyl amino pyridene introduced in 1937. Sulphanilamide, which began its career as an anti-streptococcus haemolyticus agent, later showed a beneficial action on other cocci infections. According to the experimental work done by Long of Baltimore on rats, Sulphanilamide exerts a bacteriostatic action on pneumococci. Osgood claims it has an antitoxic action also. No one can doubt that Sulphanilamide preparations do benefit the pneumonic patient. When given in large doses early, there is a decrease in the temperature, pulse and respirations within 24 to 48 hours. As Long has pointed out, we must provide an effective concentration of the drug in the blood early, continue with the maintenance dose daily and then withdraw the drug slowly only after a marked improvement is noted. Failure to do this usually results in a recurrence of the patient's symptoms and signs plus an elevation of the T.P.R. Today, we are able to estimate the blood content of the drug by colorimetric methods. An effective concentration is considered to be 10 mgm. per 100 cc. of blood. This level must be reached early and maintained daily till marked improvement is shown. To give a working idea of how the drug is given let us say we have a man weighing 150 pounds with a definite lobar pneumonia. An initial dose by mouth would be 80 grains. The maintenance daily dose is 20 grains every four hours for 24 hours. The total dose for one day would be 180 grains. This dosage is maintained until marked improvement is noted. It is then decreased slowly, i.e., 15 grains q.4.h.; 10 grains q.4.h. until it is stopped entirely.

There are a few toxic manifestations to sulphanilamide which warrant our consideration. The first group, consisting of nausea, vomiting, cyanosis and mild anaemia, is relatively unimportant. In the second group we have simple fever, dermatitis, acidosis, jaundice and acute haemolytic anaemia. The drug must be stopped if these occur. The simple fever occurs as a sharp rise in a lowered temperature during the administration of the drug. The dermatitis may imitate measles, scarlet fever or urticaria. Acidosis may be combatted by giving sodium bicarbonate in the ratio of 1:3 of the drug. The best way to control the dosage and to guard against toxic manifestations is as follows:

(1) The daily estimation of the sulphanilamide content of the blood.
(2) Daily haemoglobin estimation.

(3) Four-hourly temperature record.

(4) Careful examination of the patient.

Our second chemical agent, sulphanilyl amino pyridene, is also known by the experimental number M. & B. 693 and by the trade name Dagenan. Just as sulphanilamide is considered to be a specific anti-haemolytic streptococcus agent, so is amino pyridene considered to be a specific anti-pneumococcal agent. Two workers, Evans and Garsford, in England, are perhaps mostly responsible for the wave of enthusiasm which accompanied this drug in Canada. During the first clinical trials they observed a series of 100 cases of lobar pneumonia, using as controls 100 comparable cases receiving non-specific treatment. The mortality in the controls was 27 per cent, while the mortality in those cases receiving amino pyridene was only eight per cent.

The mode of action, as in the case of sulphanilamide, seems to be bacteriostatic. This is borne out by animal experimentation. Clinically, amino pyridene does appear to have a beneficial effect on the pneumonic patient. When given in full doses early, we have a marked drop in the T. P. R. with improvement in the patient's condition. Failure to give the drug in sufficient dosage or withdrawal too rapidly allows a recurrence of symptoms.

Dosage: Each tablet of amino pyridene contains 0.5 grams of active principle. In an adult patient, the following dosage is advised:

2 grams at once followed by 2 grams in four hours;

1 gram every four hours for thirty-six hours.

The above treatment should produce marked improvement. We then continue with 1 gram every four hours for 36 hours and complete the course with 1.5 grams per day till 20 grams in all have been given. As might be expected, the dosage must be adjusted to the individual case.

Amino pyridene also has toxic manifestations, but less so than sulphanilamide. The following symptoms are listed, *viz.*, headache, nausea, vomiting, dermatitis, simple fever and cyanosis. Nausea is very common, whereas the remainder are uncommon. Being relatively new, undoubtedly there is much to be learned concerning its use. We might, at this point, stress a few advantages of the use of the chemical agents in the treatment of pneumonia:

(1) Can be given the moment diagnosis is made.

(2) Relatively inexpensive.

(3) Readily available.

(4) Can be given orally.

SEROTHERAPY

Specific anti-pneumococcic serum was used first in 1892. It enjoyed but a fair reputation until 1924, when Felton succeeded in concentrating the antibodies to one-tenth their original volume. This did away with the severe reactions previously encountered and did much to stimulate the use of serum. In the bacteriology of the pneumococcus many

advances have been made. In 1913, the pneumococci were first divided into three specific types, I, II and III, and a non-specific group IV. Sixteen years later, this group IV was divided into 29 specific types. Today, we have 32 types of pneumococci each with its specific anti-serum. Up to three years ago, horse serum was in general use. Today rabbit serum is gradually supplanting it. Rabbit serum is more readily obtained, is less expensive, causes fewer reactions and is said to have a more penetrating action.

In the treatment of lobar pneumonia, serum has a very wide scope. 95.5 per cent of our pneumonias are caused by pneumococci. Of these, 70 to 80 per cent are caused by types I, II and III. The latter varies in that some communities will have a preponderance of types V, VII or VIII. Happily, in the commonest type, i.e., type I, the best results are obtained.

With the above interesting facts in mind, we now come to the question: How shall we proceed to treat the pneumonic patient with serum? A definite routine must be followed. A careful history and a complete physical examination are essential. Physical findings should be checked by X-rays. Blood cultures should be done at once.

Securing the Sputum—This may be done in three ways:

(1) Collecting coughed-up sputum in a sterile container.

(2) Taking a pharyngeal swab.

(3) Lung puncture.

Lung puncture is a skilled procedure wherein the bacteria are aspirated directly from the pneumonic lobe by a needle. The dislodgment of an embolus, or pulmonary bleeding, occur rarely with good technique.

Typing the Sputum—The most common and rapid method was devised by Neufeld. When combined with its specific anti-serum, and only then, the pneumococcus capsule swells markedly. A drop of sputum, a drop of Methylene blue, plus a drop of typing serum, is all that is needed. Results are obtained in five minutes.

When to Give Serum—Serum is given at the earliest possible moment. The ideal time is within 24 hours of the onset of the disease. When given within the first three days, the mortality rate from pneumonia drops from 25 to 4.8 per cent. Waiting one more day doubles the rate. It is a common belief that beyond 3 days serum is useless. Results are poorer the farther we draw away from the onset, yet, according to Bullowa, it is never too late.

Dosage—This depends on: (1) Date of commencing treatment; (2) Type of infection; (3) Age of patient; (4) Presence or absence of bacteraemia. In a type I infection, where treatment begins within the first 24 to 48 hours, 100,000 units are usually sufficient. After 48 hours the dosage must be doubled, tripled, etc., the farther we draw away from the onset. In types I, III and VII infections and many others 200,000 units are usually the minimum. In patients past 40 years of age usually we have to double the dosage. In the presence of a bacteraemia we must double the dosage from the beginning.

Method of Giving Serum—Before giving serum we must test the patient for sensitivity towards the serum employed. This may be done in three ways. The first method, the ophthalmic test, consists in placing one drop of the normal rabbit serum diluted 1:10 into the conjunctival sac. A positive reaction, read in 20 minutes, is evident by engorgement of the conjunctival vessels. The intradermal test, using 0.1 cc. of 1:10 dilution, shows up as a reddening of the skin at the site of the injection. The intravenous test, using a 1:5 dilution, 0.5 cc., is postive if the blood pressure falls 30 mms. Hg. in 10 minutes. Any patient with a positive reaction must be desensitized. Providing the sensitivity tests are negative, serum may be given. All serum is given intravenously so that we may give sufficient in the shortest possible time. The first dose varies, but at the Victoria Hospital we give 10,000 units. Great caution must be exercised here. It is usually with the first or second dose where reactions occur. To avoid these, we give the first dose along with 200 ccs. of normal saline solution. Then any reaction will be slight and easily controllable. The second dose, given in two hours, is usually 20,000 units and may be given with 20 cc. of saline. Ten minutes are taken to inject this amount. In the absence of reactions, we then give 20,000 to 40,000 units directly into the vein every two hours. This is continued till we get a marked drop in pulse rate, temperature and respirations. In some cases 400,000 to 800,000 units are needed to affect a response. Following a marked drop in the T. P. R. an additional 20,000 to 40,000 units may be given to ensure success. In the early ideal case the effect of serum is dramatic. On admission, we have a dyspnoeic, toxic and very miserable patient. Within 12 to 24 hours of serum treatment we have a quietly breathing, non-toxic and very grateful patient. Serum does not stop the pneumonic process. Indeed it is surprising how well the patient looks yet has all the signs of a consolidated lung. Biologically, the use of serum has a sound basis. Primarily, it is an anti-toxin. Secondly, it fixes the pneumococci in such a way as to render them innocuous and induces the phagocytes to complete their destruction.

As one would expect, serum therapy is attended by many reactions, varying in type and degree. Some of the common ones are chills, hyperpyrexia, shock, collapse, vomiting, dyspnoea, cyanosis plus anginal, lumbar or chest pain. Acetyl salicylic acid gr. 20 given 20 minutes prior to injection prevents chills and thermal reactions. Epinephrine min. 30 given before, during or after the reaction is an excellent drug. If reactions occur during the injection, stop at once, wait for one hour and then begin again, using diluted serum and giving it very slowly. To begin carefully and slowly usually results in a very rapid successful ending.

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Anatomy and Physiology — A Short History

By RAY STUBBING, '42

ALL history is colourful! It deals with facts and figures and with famous people; it traces the course of progress and development; it is the record of an everlasting search for truth and knowledge. The student of history becomes engrossed in the life stories of individuals, for history is not a record of geographical, mechanical or scientific facts, but rather it is a tale of the desires, actions and achievements of men and women.

This is an historical essay about the fundamental sciences of modern medicine, anatomy and physiology. Because it is a history, it deals with people; because the sciences have developed over the course of centuries, it is possible to touch only the beginnings.

ANATOMY

During the first century there arose Claudius Galen, a native of Greece, tall of stature, dark, bearded, vain of appearance, destined to become the renowned physician and medical authority of the Roman world. He dissected the bodies of animals such as dogs and pigs, and accepted the arrangement of the body structures of these animals as being that of the human body. His knowledge was essentially empirical, yet he was the outstanding healer of diseases in his time. His system of medicine and his books were to be accepted as classics for many years.

Galen's influence lasted for fifteen centuries. His system was taught in all schools, and if, as often happened during the course of a dissection, the structure of the animal did not correspond to Galen's teaching, the animal was called an anomaly. Galen was never questioned, so generally was his authority accepted. Medicine was, during that period, chiefly "according to Galen." And then suddenly, as it seems, men thrust aside both tradition and authority. They began to build a knowledge of the human body and of disease on a sound, scientific basis. Henri de Mondeville, in 1304, exclaimed, "God did not exhaust all his power in making Galen."

The Renaissance of medicine had begun. Andreas Vesalius, born in Belgium in 1514, became the founder of Gross Anatomy. He studied medicine in the University of Louvain, and from there he went to Paris which was then the centre of medical education.

Vesalius' nature made him dissatisfied with the halting approach to anatomy which his professors presented. Neither could he be sympathetic with the church's prohibitory stand on the dissection of the human body. He became a skilled dissector, and was often able to confuse the professors with searching questions regarding some structure. By stealing the bodies of executed criminals, he was able, finally, to dis-

sect and study the human body. He secured the position of Professor of Anatomy at the University of Padua, in Italy, by naming the individual bones of the human body while blindfolded. In Italy, thought and teaching were more progressive, and with the assistance of Jan van Kalkar, a pupil of the artist Titian, he published in 1543 his well-illustrated book, "De Humani Corporis Fabrica." This book revolutionized the science of human anatomy by introducing the method of direct observation.

Vesalius had several important contemporaries: Dryander of Marburg; Miguel Servetus, the Spanish theologian who dissected human bodies primarily to find the seat of the soul; Leonardo da Vinci, the artist who did human dissections in order to improve his sense of proportion in art. There were many immediate successors to Vesalius who were able to avail themselves of his work and to make further discoveries; Fallopius, and the Fallopian tubes; Eustachius, and the Eustachian tubes; Varolius, and the pons Varolii, and many others. Thus in the course of a century, the greater portion of human anatomy was investigated and explained. Sir William Osler said of Vesalius' book: "The greatest book ever printed from which modern medicine dates."

In 1590, Hans Janssen, a Dutch spectacle-maker, made a small metal tube with a simple lens inserted. He called it a flea glass. As seen through it, a flea resembled a grotesque, hairy monster. It was considered a toy but there was the germ of the microscope.

Antonj van Leeuwenhoek, born in Delft in 1632, is looked upon as the inventor of the microscope. He was an ingenious young man who devised a combination of lenses which would magnify an object to many diameters. Thus the science of microscopic anatomy (histology), and of developmental anatomy (embryology), were made possible. In 1677, van Leeuwenhoek himself reported the discovery of "little animals" in the male seminal fluid. He found the striations in muscular tissue and he discovered that scrapings from the tongue revealed countless animalcules under the microscope. Salenpatrius, in 1699, asserted that he had observed a minute human form in each spermatozoön as supporting evidence to the doctrine of of preformation. However, William Harvey, with whose work in physiology we shall later deal, had published earlier a book entitled "Studies on the Generation of Animals." It contradicted the doctrine of preformation by showing that the embryo went through stages of development until it gradually evolved the parent form. He may thus be regarded as a founder of embryology.

Marcello Malpighi, born in Bologna in 1628, was the investigator who first used the microscope as a serious scientific weapon. He was curious regarding the minute structure of the various organs of the body. On examining prepared lung tissue, he saw that the arteries which entered the tissue broke up into even finer vessels, as fine as hairs. He called them capillaries. He followed these and observed that they

gradually became larger until they formed veins. Here was a great histological discovery. William Harvey had earlier proved that blood left the heart by arteries and returned by veins. But how did it get from the arteries to the veins? Malpighi supplied the answer.

Malpighi did not stop until he had thoroughly established the science of histology. From his investigations of the spleen, we have the Malpighian bodies; of the skin, we have one layer called the rete Malpighii; of the kidney, we have the cortex and the renal pelvis. From his studies he was able to assume correctly that the kidneys extracted urinous elements from the blood.

Great strides were now possible in the treatment of diseases, and in the progress of medical science, because of these developments in gross, microscopic, and developmental anatomy.

PHYSIOLOGY

Towards the end of the 16th century a young Englishman entered the University of Padua, made famous for its anatomy by Vesalius. He was William Harvey, who was to establish the true facts of blood circulation, and thus to create the beginnings of physiology.

Various fanciful theories existed. Galen had observed that after death the arteries contain air and the veins blood. So he had advanced the statement of a circulation depending on the passage of blood in the veins and air in the arteries; the flow of blood through minute orifices in the interventricular system; with the liver, as well as the heart, a pumping-organ. Vesalius had had serious doubts about the correctness of this view yet he was unable to improve upon it.

William Harvey is rightly given the credit for establishing the true facts of circulation: that the blood travels in a circle. However, it is interesting to observe that Miguel Servetus had already described the circulation of the blood from the right to the left side of the heart in "The Restitution of Christianity," published in 1553. Servetus was a radical theologian and the heretical views which he expressed led to his being burned at the stake in the same year, and to the destruction of the five hundred copies of the book. Several copies were preserved, but it was not until 141 years later that medical attention was called to his descriptive explanation of the circulation.

Harvey conducted numerous experiments in the early years of the 17th century. He tied off the artery of a sheep and made a nick in it on the side toward the heart. Blood spurted with each heart-beat until gradually no more flowed. He reasoned that none was returning to the heart. He tied off a large artery close to the heart and watched that organ become engorged until all the blood had gathered in it. He chose a vein in the arm and "milked" it toward the heart, watching it rapidly fill up again from the extremity. So he showed the direction of flow in the veins and arteries, and thus logically observed that the blood travelled in a circle which led from the heart to the lungs and back

again. We have seen how the discovery of capillaries later substantiated his work. These results were published in 1628 as "Anatomical Exercises on the Motions of the Heart and Blood in Animals." It ranks in medical importance with the anatomical publication of Vesalius.

Harvey had enunciated the first major generalization of physiology. It was of great significance because it demonstrated the value of the experimental methods; it made possible the control of haemorrhage in surgery; it explained the function of the placental after-birth; and it permitted further progress in the physiology of the various organs of the body.

The second major problem of physiology was to explain the function of respiration, and numerous men made discoveries which finally led to its solution. In 1657, Robert Boyle exhibited to the "Philosophical Associations" at Oxford an apparatus which demonstrated that air has weight, so that if air were pressed against a column of mercury, the level of the column would rise. Robert Hooke, in 1667, showed that the act of respiration is of secondary importance, and John Mayhow, in 1668, demonstrated the mechanism of respiration. In a pamphlet, "Tractatus de Corde," he explained that venous blood is changed to bright red arterial blood because of the air mingling with it. Gradually men were approaching the truth.

Chemistry at last supplied the answer. Joseph Priestly, a Unitarian minister, actually isolated a gas which is necessary for all combustion, and he called it "phlogiston." Finally a brilliant French chemist, Lavoisier, in 1777, isolated oxygen from the air and explained correctly how the blood conveys oxygen to the body tissues and takes up carbon dioxide in exchange.

The progress of physiology was most rapid. By the middle of the 19th century investigators had discovered the function of digestion, the nature of muscle contraction and of nerve impulses, and the process of excretion. Since then the great unifying principle of nutrition has been explained.

Medicine has come a long way since the time when the discoveries of Vesalius and Harvey gave impetus and direction to the major sciences. Medical science and practice are now recognized as necessary accompaniments to any real social progress, and the application of medical knowledge to the health of a community is slowly becoming the concern of all people.

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Abstracts

HUMAN STERILITY

By W. P. TEW

Can. Med. Assn. J.; 40:116, 1939

A thorough and comprehensive account of the main features of human sterility is given. The author has indicated that sterility is the result of not one but several factors and that usually both parties are partly at fault. The general factors influencing human infertility: race, age, climate and season, civilization and constitution, are listed and briefly discussed. An excellent clinical classification of sterility based on etiology and a method of investigating a sterile mating are outlined. The treatment of infertility in both the female and the male are outlined.

—R. JOLLIFFE, '41.

OBSERVATIONS ON THE NEUFELD REACTION (QUELLUNG TEST) FOLLOWING DESICCATION OF PNEUMOCOCCUS PREPARATIONS

By H. R. BROWN

Jour. Lab. Clin. Med., 23, 12, 1938

A method of preparing dried smears of sputum, and also of using dried smears of type-specific sera, is herein described. By this method loss of time in detecting the presence of a specific type of pneumococcus can be avoided, and danger of destruction or damage by capsular change to the specimen by autolysis or contaminating overgrowth of other bacteria can also be obviated. A very comprehensive series of experiments shows that dried smears of sputum containing pneumococci will give positive Neufeld reactions after being exposed either to high or low temperatures for periods of a year. It is also shown that specific sera may be dried on slides at room or incubator temperature and used whenever desired. The Quellung reaction develops as well as, or better than, in cases where the less simple method of using liquid sera is used.

—J. G. STAPLETON, '41.

TREATMENT OF PNEUMONIA WITH 2 (P. AMINOBENZENESULPHONAMIDO)-PYRIDINE

By G. M. EVANS and WILFRED S. GARSFORD

J.A.M.A.; 108:1483, 1937

The authors administered this drug in one hundred cases of lobar pneumonia and forty cases of broncho-pneumonia. As a result the mortality rate dropped from 27% in control cases which did not receive the drug to 8% in the test cases which did receive the drug.

Method of Administration: At the beginning the dosage was largely experimental. A common practice was to give one tablet (0.5 grams) every four hours for three or four days, followed by one tablet twice a day for an additional two or three days. The average amount given per case by this method was 12 grams. Later larger initial doses were given. At the same time a close watch was kept on the blood count for signs of a granulocytopoenia. Doses as large as four tablets (two grams) were given on admission, followed by one tablet every four hours. The average amount given per case by this method was 25 grams. In a few cases as much as 9 grams has been given in the first 24 hours. The temperature and toxic symptoms, especially the delirium, subsided very rapidly.

Toxic symptoms were not pronounced and cleared up immediately upon withdrawal of the drug. Cyanosis appeared in 25% of the intensely treated cases. Spectroscopic examination of the blood showed a methhaemoglobinaemia in 6% of the cases.

No cases of sulphhaemoglobinaemia were encountered.

—D. WOLLIN, '39.

CONTROL OF PUERPERAL FEVER

By L. COLEBROOK

B.M.J.; 4069:1378, 1938

Dr. Colebrook pointed out that approximately 40 per cent of the cases of puerperal fever are brought about by the

haemolytic streptococcus, the source of infection in at least 50 per cent of cases being an attendant contact—that is, doctor, nurse, or midwife. Other sources of infection include members of the mother's household and the mothers themselves. Respiratory infections are probably the chief offenders.

Dr. Colebrook listed the following preventive methods:

1. The wearing of efficient masks by attendants.
2. The use of strict antiseptic toilet, in the attaining and maintaining of which soap and water are of prime importance.
3. The use of iodine and dettol as antiseptics.
4. Institutional confinements rather than home confinements. (In four years at Queen Charlotte's, only one patient in 700 had developed haemolytic streptococcus infection, whereas in that district the incidence had been one in 135).

In discussing active therapeutic measures, Dr. Colebrook contented himself with outlining the remarkable drop in the death rate in puerperal fever at Queen Charlotte's following the introduction of sulphanilamide therapy.

—H. T. McALPINE, '39.

DIVERTICULITIS OF THE SIGMOID COLON

By J. H. GEDDES

Can. Med. Assn. J.; 40:157, 1939

The author has dealt briefly but comprehensively with the main aspects of diverticulitis of the sigmoid colon. He has divided the condition into five clinical groups. The importance of prophylactic treatment in the first group, diverticulosis, to prevent progression of the condition to symptomatic diverticulitis is indicated. The necessity for prolonged bed rest in the acute phase is stressed and the medical treatment of this phase outlined. The indications for surgery in the complications attending diverticulitis of the sigmoid colon are noted with the necessity for skilled surgery. As the author has pointed out, the development of carcinoma in diverticulitis, though rare, is possible and with all carcinoma of the sigmoid must be differentiated from the hyperplastic stenosing type of diverticulitis. The differential diagnosis of these two conditions with the difficulties encountered is thoroughly discussed.

—J. GALLOWAY, '40.

TEACHING OF MEDICAL ECONOMICS TO UNDERGRADUATE MEDICAL STUDENTS

By KINGSLEY ROBERTS and MICHAEL M. SAIRS

J. Assn. of Amer. Med. Colleges; 13:359; 1938

The results of an inquiry made to 64 medical schools in Canada and the United States regarding the teaching of medical economics are here analyzed.

Forty per cent of the schools give no attention to the subject, while in the others it is handled in various ways. Of these remaining 37 schools, 15 give a series of several lectures on phases of medical economics and ethics; 6 schools reported a rather systematic course entitled "Medical Economics"; 8 schools are giving a broader course dealing with the economic and social relations of the medical services. Only 4 schools were offering a really comprehensive lecture and discussion course dealing with medical ethics, the economics of medical practice and various studies of socialized medicine.

The article shows that about one-half of the medical schools are paying serious attention to teaching of medical economics and that attention to the teaching of this important subject is on the increase.

—RAY STUBBING, '42.

THE TREATMENT OF PARALYTIC BLADDER IN CASES OF SPINAL CORD INJURY

By F. HINMAN

Surgery; 4:649, 1938

Four phases characterize the common effect on micturition of a transverse lesion at any level of the cord: (1) retention, (2) overflow incontinence, (3) automaticity, (4) true incontinence. In cases of fracture above the lumbar center the first three occur in succession; an automatic bladder never develops as the late and final effect after fractures below this center, and incontinence may follow destruction of the cord at this level.

Injudicious treatment of the paralyzed

bladder results in urinary infection and bed sores and will foil the outcome to a maximum of over 80 per cent. The intent of all care, therefore, is to prevent or control these two evils. Treatment should be based on sound urological principles and it is impractical to treat all paralyzed bladders alike. The accepted methods are:

(1) *Noncatheterization and Manual Expression:* Pressure should be applied regularly every 6-8 hours with the open hand above the symphysis. This will ward off urinary sepsis and if successful will hasten automaticity.

(2) *Suprapubic Cystostomy:* This method gives good drainage and tidal irrigations may be given through it or suction applied on occasion.

(3) *Retention Catheter with or without Tidal Irrigation:* Continuous care and attention is required for a retained catheter; if this is possible a retention catheter may save time, control the infection and keep the patient dry and comfortable until such time as automaticity develops. It must be emphasized that all authorities condemn intermittent catheterization.

—CLEMENT DELETSKY, '40.

VARICOSE ULCERS AND INSULIN

By L. G. PAYNE

Can. Med. Assn. J.; 38:269, 1938

Varicose ulcers are not uncommonly encountered in general practice, their most important aspect being treatment.

There are many methods of treatment, most of them dating back to many years ago—rest with elevation of the leg: antiseptic powders and salves, various ointments, and occlusion of adjacent veins. Local treatment with insulin has a definite value. Apply to the ulcer, cleansed with saline compresses and dried, a small amount of insulin (usually U20 strength) for approximately 20 minutes. Then the insulin which has not been absorbed is removed, the base of the ulcer dried again, and the dressing applied. Repeat three to four days, and keep leg elevated.

In younger persons, or where the margin is deep or the base fibrosed, the treatment is less satisfactory, and requires infection or ligation of the regional veins.

Where the ulcer is shallow, the patient older, or rest with elevation impossible, insulin gives the best results. For the initial treatment where it is usually infected, dressing of iodine dusting powder, covered by elastic adhesive for three days, is good.

—L. C. BARTLETT, '41.

OBSERVATIONS ON THE TREATMENT OF EMPYEMA IN CHILDREN

By H. L. WALLACE

B.M.J.; 4053:560, 1938

The author has investigated the treatment of empyema in 348 children admitted to the Royal Edinburgh Hospital for Sick Children, over a period of fifteen years. He has attempted to compare the radical and conservative methods of treatment.

The conservative treatment consisted of repeated aspiration, drainage by cannula aspiration, and drainage by closed suction. The radical treatment consisted of thoracotomy with open drainage and drainage by rib resection. The most striking and significant difference is in the children under two years of age. By conservative methods, the mortality was 57.4 per cent, and by radical methods the mortality was 37.1 per cent. This is significant in that this age group usually is treated by conservative methods. The mortality, using radical treatment, in the age group from two to five years of age was slightly lower, and in the age group from five to twelve years of age was slightly higher than by conservative treatment.

The other factor investigated was the duration of stay in hospital. The cases treated by conservative methods averaged from eight to fourteen weeks, depending upon the method used. The cases treated by radical methods averaged five weeks.

In conclusion, the author deduced from this series of cases that the best treatment was the operation of rib resection performed immediately after localization of the empyema had been achieved by means of repeated aspiration. It is emphasized that the ideal treatment has not yet been evolved, and that no finality has been reached on this important problem.

—R. H. CRAM, '41.

TREATMENT OF INFECTED WOUNDS WITH UREA

By L. F. MULDAVIN and J. M. HOLTZMANN

Lancet; 234:549, 1938

Urea in saturated solution has a solvent power on slough or debris which, being removed, prevents a potential breeding ground for bacteria. In addition, solutions of 8 - 25% are found to be bacteriostatic and stronger solutions are bactericidal.

It was used with success in abscesses, carbuncles, whitlows, cellulitis, infected burns and wounds. The technique consists of syringing away free pus and necrotic material with a saturated solution of urea, excessive moisture removed and urea crystals then liberally applied. Waxed paper is placed next to the crystals to keep them in contact with the wound and to prevent dressings from becoming soaked. Adjacent skin is protected with zinc cream.

The disadvantages of the treatment are:

(1) pain is sometimes experienced on application.
(2) urea does not directly stimulate epithelialisation.

Results were so encouraging that it has been adopted as routine treatment of infected wounds in the casualty department of the Royal Free Hospital.

—D. STATE, '39.

THE TREATMENT OF BACILLARY DYSENTERY WITH BACTERIOPHAGE

By J. E. MURRAY

The Practitioner; cxli, 199, 1938

The author treated 146 cases of bacillary dysentery. The majority were cured within two weeks. The bacteriophage used must act on all dysentery groups—Shiga, Flexner, and Sonne. Four patients suffered from the same complaint for two successive summers, but probably represented cases of re-infection. Bacteriophage does not confer immunity like vaccine. The author points out that many cases of chronic colitis are really bacillary dysentery, and should be investigated by a bacteriologist. The incidence is seasonal and greatest from July to September. The treatment was one ampoule of bacteriophage in alkaline medium before meals. The diet should be nourishing, fluid and fat-free, containing no red meat, alcohol, or seedy fruits. The author concludes that bacteriophage is the best treatment for bacillary dysentery and that thereapeutic failures are due to an unreliable bacteriophage.

—A. JOHNSON, '40.

DISLOCATIONS AND FRACTURE DISLOCATIONS OF THE PELVIS

By R. WATSON-JONES, Liverpool

Brit. J. Surg. 25; 773-781, 1938

The author divides fractures of the pelvis into injuries not involving the pelvic ring, e.g., fractures of the crest and spines of the ilium, fractures of the acetabulum, etc., and fractures involving the pelvic ring. He then goes into a consideration of the various types of injury to the pelvic ring and for each type gives the method of treatment which he has found to be most satisfactory.

Various types of injury to the pelvic ring mentioned are:

(1) *Isolated Injuries:* Include fracture of the body of the ilium, unilateral fracture of one or both pubic rami, and slight separation of the symphysis pubis. In this group, since there cannot be serious displacement, no treatment is required except recumbency in bed for a few weeks; immobilization is unnecessary.

(2) *Combined Injuries of Pubic Segment of the Pelvic Ring:* Both fractures in anterior segment of pelvic ring, e.g., bilateral fracture of both pubic rami. These injuries are produced by compression of the pelvis in its lateral axis. The displacement is limited, due to the large amount of muscular attachment in this area. The patient is to be treated in recumbency lying on his back for four to six weeks.

(3) *Combined Injuries of Iliac and Pubic Segments of the Pelvic Ring:* These injuries cause complete disruption and wide displacement. They are produced by antero-posterior compression of the pelvis. The displacement is most easily corrected by manipulation in lateral recumbency and the application of a double plaster spica. The patient must lie on one side and not on his back. The functional result depends on the accuracy of reduction of the sacro-iliac dislocation, which may easily be overlooked.

—N. J. ENGLAND, '39.

Editorial

CANCER IN NEON LIGHTS

Statistics show that cigarette sales vary directly as the amount of advertising done per year. Of the three most popular brands offered for sale in the United States, the one that has the most advertising is invariably the leading cigarette of that year. If you wish to sell something to somebody you must keep it before their attention. If you wish to sell cancer treatment to the public you must let them know about it. For this reason the Canadian Society for the Control of Cancer was formed.

Recent surveys have shown that hope for *immediate* improvement of cancer mortality lies in education of the public. It is granted that ultimately the ideal and only true way to eradicate cancer is through research. However, before the benefits of this field become available many thousands of people will have died of the disease.

Radiation and surgery are now accepted as the only measures of proven value in the treatment of cancer. The earlier the lesion is demonstrated and treated, the better the patient's chance becomes of cure. It is then essential that the patient comes to the doctor early; that the doctor make an immediate tentative diagnosis; and that treatment be started without delay. Of these three links in the chain of successful cancer therapy, the first two can be greatly improved. By education, the patient can be taught to recognize cancer early. Education is best carried out by keeping before the public the early signs and symptoms of cancer. Thus women would realize the significance of a painless single nodule in the breast; men would appreciate the importance of a change in gastric habit. It would then be up to the physician to institute treatment early.

Doctors throughout the province have already indicated their interest and enthusiasm for this new organization. An Ontario Society for the Control of Cancer has been formed to act in conjunction with the Canadian Society. It is expected that local Lay-Medical organizations will be set up in all the cities and towns of Ontario. Three of these have already been organized and plans to circularize the public have been started. If there is not a local society in your community already there should be one soon. For information write Dr. C. C. Ross, Secretary, Canadian Society for the Control of Cancer, 43 St. George St., Toronto.

Book Reviews

THE BRAIN AND ITS ENVIRONMENT

By JOSEPH BARCROFT,

Professor of Physiology, Cambridge.

(111 pp., $2.00. Yale University Press, 1938.)

This book represents the script of the Dwight Harrington Terry Foundation Lectures delivered by Professor Barcroft at Yale University. An attempt has been made to correlate central nervous system activity with the physical and chemical state of the blood passing through the cerebral circulatory system. The story is told in a vivid and entertaining manner. Chapter III, dealing with the relation of mental efficiency to properties of the blood, will stimulate many new lines of thought. The volume is small and is recommended as a "week-end book" to those especially interested in the nervous system.

DIABETES INSIPIDUS AND THE NEURO-HORMONAL CONTROL OF WATER BALANCE — A CONTRIBUTION TO THE STRUCTURE AND FUNCTION OF THE HYPOTHALAMICO-HYPOPHYSEAL SYSTEM

By C. FISHER, PH.D., W. R. INGRAM, PH.D.,
and S. W. RANSON, PH.D., M.D.

Institute of Neurology, Northwestern Univ. Medical School, Chicago.

(212 pp., Illustrated, $5.00. Edwards Bros., Ann Arbor, 1938.)

This monograph sets forth in detail the results obtained during several years of intensive research on the anatomy and physiology of the hypothalamus. Working chiefly with the cat and monkey, circumscribed lesions were placed in various parts of the hypothalamus with the aid of the Horsely-Clarke stereotaxic instrument. When such lesions involved the hypophyseo-hypothalamic tract, diabetes insipidus invariably resulted. Interruption of the nerve fibres passing between the hypothalamus and the hypophysis produced profound degeneration of the posterior lobe of the latter. The pars intermedia and pars anterior were not affected.

In female animals with experimental diabetes insipidus partuition was also disturbed, presumably due to a deficiency in the elaboration of the oxytocic hormone.

These authors have amply demonstrated the close anatomical and physiological relationship between the hypothalamus and the hypophysis. The monograph is printed by a process of photolithography with excellent reproduction of the type-script and illustrations.

—M. L. BARR, M.D.

DISEASES OF THE NOSE, THROAT AND EAR

By W. H. WALLACE MORRISON, M.D.,

Clinical Professor and Chief of Clinic, Department of Otolaryngology, New York Polyclinic Medical School and Hospital.

(675 pp., 629 Illustrations, Indexed, $5.50. W. B. Saunders Co., Philadelphia, 1938.)

Dr. Morrison's is an extremely satisfactory text on this subject. Written, as the author states, out of fifteen year's experience as a teacher of graduate students, it is intended for the undergraduate student and general practitioner. The conciseness and simplicity of exposition coupled with a completeness of material renders the book of great practical value.

The treatment of each disease has been evaluated, and only those measures that have proven successful described. Every procedure is described in detail. A bibliography at the end of each chapter renders available ready access to the researches upon which the statements in the book are based.

A striking feature about the book is the abundance and clarity of the illustrations, the simplicity of which renders them extremely effective. It is interesting to note that they are all the work of the author himself. They are line drawings showing not only anatomy and pathology, but the exact technique of both diagnostic and therapeutic procedures.

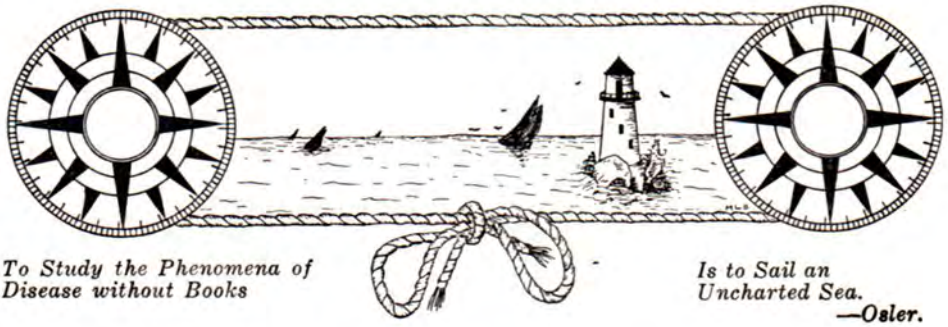
These attributes insure a wide popularity for the book.

—J. GALLOWAY, '40.

EDITOR'S NOTE: Dr. Morrison is a graduate of the University of Western Ontario Medical School, Class of '19.

SURGICAL "BELIEVE-IT-OR-NOTS"

A post-mortem recently performed on an English woman disclosed a pair of forceps left in the body thirteen years before. A jury completely vindicated the surgeon of any charges of negligence.



To Study the Phenomena of Disease without Books

Is to Sail an Uncharted Sea.
—Osler.

RECENT ACCESSIONS TO THE MEDICAL SCHOOL LIBRARY

American Association for the Advancement of Science—Tuberculosis and Leprosy, the Mycobacterial Diseases. 1938.
Association for Research in Nervous and Mental Disease—The Pituitary Gland; An Investigation of the Most Recent Advances. 1938.

Berkeley, Bonney and MacLeod—The Abnormal in Obstetrics. 1938.
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Rosanoff—Manual of Psychiatry and Mental Hygiene. 7th ed. 1938.

Schilder—Psychotherapy. 1938.
Sharpey-Schafer—Experimental Physiology. 6th ed. 1938.
Shryock—The Development of Modern Medicine. 1936.

Wakeley & Orley—A Text-book of Neuro-radiology. 1938.
Walker—The Primate Thalamus. 1938.
White—William Alanson White; the Autobiography of a Purpose. 1938.

SUBSCRIPTIONS:—

American Journal of Medical Jurisprudence.
Anesthesia Abstracts.

British Heart Journal.

Canadian Science Digest.

Enzymologia.

BLOOD DONORS

Like innumerable other things, that medical miracle — blood transfusion — has its titleholders.

A Parisian has put a claim on the world championship with the boast that he has given transfusions 264 times, a total of 13.5 gallons, though the normal body has only five quarts. An American presents evidence he has given 125 quarts in more than two hundred transfusions since 1914 — for a total of five thousand dollars, incidentally.

Scattered statistics on transfusion change rapidly, but it is certain that among the bona fide "champions" on the receiving end is a fourteen-year-old New York boy who had 89 operations, at least 83 recorded transfusions. To combat a disease which impaired his ability to manufacture blood, a nine-year-old North Carolinian has taken others' blood regularly for six years, and leads his class in school. A man in Missouri had more than a hundred transfusions within a year.

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Miller, J. A.: The Pathogenesis of Bronchiectasis. J. Thor. Surg.; 3; 246-269; 1934.

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